IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s)	: Mermelstein et al.	Customer No.	: 62965
Serial No.	: 10/729,869	Confirmation No.	: 8490
Filed	: 12/05/2003	Group Art Unit	: 1614
Examiner	: Kwon, Brian Yong		
For	: NMDA Receptor Antagonist Formulation with Reduced Neurotoxicity		

DECLARATION OF DONNA MADDEN UNDER 37 CFR 1.132

The Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

I, DONNA MADDEN, do hereby declare and state as follows:

1. I am a citizen of the United States and am more than twenty-one years of age.

2. I am currently employed by Javelin Pharmaceuticals Inc. (Javelin), assignee of the above-captioned application and the party in interest, as the manager of non-clinical affairs. I received a B.S. in Biology and an M.S. in Toxicology. I have worked as a research scientist in the pharmaceutical industry for over ten years and have monitored and directed numerous preclinical studies. I consider my main area of therapeutic knowledge to be pain management. A copy of my Curriculum Vitae is attached hereto as Exhibit 1.

3. I am not an inventor of the above-captioned patent application, but have been asked to sponsor the studies described herein on behalf of Javelin for the purpose of obtaining data to support patentability of the claims of this application.

4. I have read and am familiar with the application as it was filed in the U.S. Patent and Trademark Office (the "USPTO"), the pending claims of the application, and the

Office Action mailed by the U.S. Patent and Trademark Office on January 23, 2006 in connection with the application.

5. I understand that the claims of the pending application have been rejected by the Examiner as anticipated by WO 98/51282 (Unger) and Collier et al. (WO 00/24396) and/or obvious over GB1330878 (Bristol Meyers Co.) in view of Williams et al. (U.S. 6638981 B2). I have read and am familiar with these references. I understand that the examiner has taken the position that the prior art disclosure of formulations of ketamine with benzethonium chloride renders obvious the claimed formulations of ketamine with benzalkonium chloride.

6. I designed and sponsored a comparative neurotoxicity study of formulations of ketamine with these different preservatives that was conducted by Charles River Laboratories. Specifically, I have been asked to compare the neurotoxic effects of ketamine benzalkonium chloride (claimed in the present invention) against ketamine benzethonium chloride when the preservative is present in each formulation at a lower dose than that employed in the approved and commercially available KETALAR®.

7. In order to compare the neurotoxic effect of these formulations, the following study was conducted. The following five formulations were tested:

(1) Saline
(2) Ketamine 10% + benzalkonium chloride 0.002% + sterile water
(3) Ketamine 15% + benzalkonium chloride 0.002% + sterile water
(4) Ketamine 10% + benzethonium chloride 0.002% + sterile water
(5) MK-801

8. Saline served as placebo and MK-801, a known NMDA receptor antagonist associated with neuronal and axonal degeneration in the retrosplenial cortex of the brain, served as a positive control.

9. Two formulations containing benzalkonium chloride and different concentrations of ketamine, 10% and 15% were tested. These concentrations were chosen because they represent anticipated commercial concentrations.

10. The formulations were tested for induction of neuronal degeneration in the retrosplenial cortex of the brain upon subcutaneous administration. A single subcutaneous injection was given above the scapular region to 10 rats per group (5 female and 5 male). Histology was performed on Study Day 2 at 24 hours post-dose and neurological damage was evaluated.

11. The following chart contains a synopsis of the test results of the above described study. *See also* Charles River Laboratories Final Pathology Report, Study Number JIR00009, May 24, 2006, attached hereto as Exhibit 2.

Treatment[a]	**Total Dose**[b] **(mg/kg)**	**Treatment Related Lesions**[f] **(% Incidence)**	**Single Degenerative Neuron Incidence**	
			%	**Absolute Number**
Saline	0	ND	10[g]	1 of 10
Nasal Ketamine Formulation 1[c]	60	ND	ND	0 of 10
Nasal Ketamine Formulation 2[d]	60	ND	10	1 of 10
(Combined data for the Ketamine groups)[h]			5	1 of 20
Ketamine benzethonium chloride	60	ND	20	2 of 10
MK-801[e]	0.5	50	NA	

[a] Preservative concentration of both benzalkonium chloride and benzethonium chloride was 0.02 mg/mL (0.002% w/v) (benzethonium chloride concentration in marketed Ketalar is 0.1 mg/mL)
[b] Total dose of ketamine or MK-801
[c] Formulation 1: PMI-100 (10% ketamine)
[d] Formulation 2: PMI-150 (15% ketamine)
[e] An NMDA antagonist used as a positive control containing no preservative
[f] Minimal to mild neuronal degeneration within the retrosplenial cortex of the brain
[g] Degenerative neuron in the temporal cortex
[h] These data represent a combination of the 10% and 15% Ketamine formulations.
ND: none detected
NA: not applicable
Each treatment group consisted of 5 female and 5 male rats

12. The MK-801 rats exhibited significant neurotoxicity typical of NMDA receptor antagonists detected in the medial area of the retrosplenial cortex with an observed

50% incidence. These definitive neurotoxic lesions are known as classic treatment related lesions (TRLs). Definitive TRLs were limited to the female rats treated with MK-801. These females had the expected pattern of neuronal degeneration within the medial aspect of the retrosplenial cortex.

13. There were no classic NMDA TRLs observed with any of the ketamine formulations.

14. In comparing the ketamine formulations, the greatest incidence of single neuronal degeneration was observed with the formulation containing ketamine in benzethonium chloride. This incidence was up to four-fold greater than that of ketamine containing benzalkonium chloride and two fold greater than observed with saline alone. These results suggest that the formulation of ketamine with benzalkonium chloride has reduced neurotoxicity relative to the formulation of ketamine with benzethonium chloride.

15. Administration of an anesthetic formulation that demonstrates markedly fewer occurrences of degenerative neuron incidence is more acceptable from a toxicological standpoint than a formulation with greater neurotoxicity. This is particularly so with a class of compounds, such as NMDA receptor antagonists, which have been found to have neurotoxic effects.

16. The Final Pathology Report, described in paragraph 11 above, also concluded that "higher frequency of neuron degeneration within the benzethonium chloride preservative group ... suggests that benzalkonium chloride may be inherently less toxic than benzethonium chloride." See Exhibit 3, page 3, last paragraph.

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17. I hereby declare that all statements herein are based on information and belief and are believed to be true and that these statements were made with the knowledge that willful false statements made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of any patent issuing from the above-captioned patent application.

Date June 20, 2006

Donna E. Madden

Donna Madden
Manager Non-Clinical Affairs
Javelin Pharmaceuticals

Donna E. Madden
157 Fox Road
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Summary: I would like to take my Master's degree in Toxicology and my 10+ years in the pharmaceutical industry ranging from Manufacturing to Research and Development and apply it to an exciting and challenging position in a Research and Development setting. I have independently monitored/directed numerous preclinical studies (toxicokinetic, pharmacokinetic and metabolism) where I initiate and close-out the study, collect, review and process documents pertinent to the study. I have experience with the IND/NDA approval process and have written and reviewed such regulatory documents (IND, NDA, annual updates) as well as knowledge of all Clinical phases. I have calculated metrics using WinNonlin and written all the respective reports. The main therapeutic area of knowledge is pain management from Preclinical to post market. Worked for a brief period editing oncology clinical protocols, revising clinical SOP's, verifying CRFs, organizing and collecting core documents for the clinical and client site binders. I have strong written and interpersonal skills, as well, a thorough understanding of Regulatory requirements (21CFR and FDA/ICH guidelines). I am very detailed oriented, self motivated and have strong moral and ethical values.

Employment

June 13, 2005 – Present Javelin Pharmaceuticals, Cambridge, MA

Manager, Nonclinical Affairs

- Provide hand-on leadership for developing, planning and implementing Nonclinical development programs through to global registration and approval.
- Provide expertise and support as the Nonclincial representative for the product candidate development teams.
- Design, coordinate and implement Nonclinical programs by generation and review of study outlines, protocols, analysis and review of data and finalization of reports.
- Select and manage CRO's to perform studies, their activities and monitor the progress.
- Facilitate and coordinate with the development teams the Nonclinical sections of regulatory submissions including IND's, EOP2 packages, CAC packages, NDA, MAA filing and annual reports
- Draft abstracts and publications. Prepare for and lead the presentations of Nonclinical data at scientific conferences, symposia
- Supports CEO, CFO, COO by providing monthly/quarterly reports and presentations for Board of Directors meetings, Investor Relations Team.

November 9,1998 – September 30, 2004 Purdue Pharma L.P., Ardsley, New York

1/1/2003-9/30/04 **Research Scientist**
Preclinical PK/ADME
PKDM Department Purdue Pharma, LP

- Independently carry out technical and administrative responsibilities associated with the generation of bioavailability/pharmacokinetic/ disposition data using pharmacokinetic (PK) analysis techniques (WinNonlin software)
- Responsible for the design, execution and interpretation of project specific TK/PK/ADME studies
- Monitor and or direct numerous studies
- Write and finalize preclinical protocols and study reports
- Review peer reports and scientific literature
- Support multiple NDSE (Toxicology) studies, contracted TK/PK/ADME studies and in house in vivo experimentation in animals through PK and toxicokinetic (TK) analysis of ADME and TK studies
- Coordinate and oversee all activities conducted at CRO's
- Prepare TK/PK/ADME section of IND and NDA annual updates and provide support for regulatory update on assigned regulatory submission
- Provide preclinical PK support for NCE development projects
- Write and update SOPs as needed in support of Preclinical PK Group activities
- Perform GMP compliance assessments on Packaging components and Participate on the Enhanced Batch Disposition Team at our Manufacturing Site (see additional assignment)

Additional Assignment at Purdue Pharma (Jul 2003 – Dec. 2003) **Auditor - Manufacturing Quality Assurance**

- Additional assignment at the Purdue manufacturing facility (P.F. Labs – Totowa, NJ) in preparation for FDA audit
- Enhanced batch disposition audit and release of tested raw material and packaging components for GMP pharmaceutical manufacturing
- Product quality assessment of the packaging components system of various pharmaceutical finished product
- Maintain support of major responsibilities in PDKM at Ardsley site during assignment in Totowa

1/1/2001-1/1/2003 **Associate Senior Scientist**
Preclincial PK/ADME
PKDM Department Purdue Pharma, LP

- Independently carry out technical responsibilities associated with the generation of bioavailability/pharmacokinetic/ disposition data using pharmacokinetic (PK) analysis techniques
- Monitor preclinical studies
- Responsible for the design, execution and interpretation of project specific TK/PK studies
- Prepare preclinical study reports
- Support multiple NDSE studies, contracted TK/PK studies and in house in vivo experimentation in animals through PK and toxicokinetic (TK) analysis of ADME and TK studies
- Prepare toxicokinetic section of IND and NDA annual updates

9/27/99-1/1/2001 **Scientist**
PKDM Department Purdue Pharma, LP

- Perform pharmacokinetic and toxicokinetic analysis and report data from preclinical studies
- Support NDSE studies, contracted TK/PK studies and in house in vivo experimentation in animals
- Prepare preclinical study reports

11/9/98-9/24/99 **Stability Administrator/Technical Data Analyst**
PA Department Purdue Pharma, LP

- Coordinate and perform all aspects of the stability program
- Coordinate the Instrument Calibration program for the department
- Oversee and administer in-house reference standards and reference materials
- Perform internal technical data audits
- Interact with contract laboratories
- Ensure that the R&D Pharmaceutical Analysis department is following cGMP/GLP and SOP compliance following CFR, FDA and ICH regulations and guidelines

1995 - 1998 Novartis Pharmaceuticals, Suffern, New York

1995-1998 **Scientist**
Novarits Pharmaceuticals (formerly Ciba-Geigy Pharmaceuticals)

- Perform analytical testing on finished bulk products according to USP/NF and FDA requirements

- Comply with cGMP/GLP and departmental SOP's
- Perform IQ, OQ and PQ on laboratory equipment
- Maintain and update departmental SOP's
- Perform training on instrumentation and/or analytical procedures
- Liaison for laboratory move/relocation
- Instrument experience: HPLC, GC, TLC, dissolution, UV FTIR and X-ray diffraction

1994 - 1995 Lab Support, White Plains, New York

1994-1995 **Analytical Chemist at Beiersdorf, Norwalk, CT (contracted by Lab Support)**

- Technical and equipment include: basic wet chemistry – saponification value, acid iodine value, peroxide value, FTIR, density meter, refractometer, moisture content analysis

Education

2000 **Master's degree** in Toxicology
St. John's University
Honors: Rho Chi Pharmaceutical Honor Society

1993 **Bachelor's degree** in Biology with a Chemistry minor
Pace University
Honors: Tri Beta Biological Honor Society, Dean's List, Phi Eta Sigma Honor Society

Memberships

MASOT, AWIS, AAPS, New York Academy of Sciences

CHARLES RIVER
LABORATORIES
Preclinical Services

FINAL PATHOLOGY REPORT

A NON-GLP SINGLE DOSE COMPARATIVE NEUROTOXICITY STUDY of a 10% and 15% KETAMINE FORMULATION with BENZALKONIUM CHLORIDE and a 10% KETAMINE FORMULATION with BENZETHONIUM CHLORIDE ADMINISTERED by SUBCUTANEOUS INJECTION to RATS

CHARLES RIVER LABORATORIES PRECLINICAL SERVICES - OHIO
STUDY NUMBER: JIR00009

May 24, 2006

PREPARED BY

CHARLES RIVER LABORATORIES, PATHOLOGY ASSOCIATES - MARYLAND

FOR THE TESTING FACILITY

CHARLES RIVER LABORATORIES PRECLINICAL SERVICES, OHIO

SPENCERVILLE, OH

AND THE STUDY SPONSOR

JAVELIN PHARMACEUTICALS, INC.

CAMBRIDGE, MA

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FINAL PATHOLOGY REPORT

A NON-GLP SINGLE DOSE COMPARATIVE NEUROTOXICITY STUDY of a 10% and 15% KETAMINE FORMULATION with BENZALKONIUM CHLORIDE and a 10% KETAMINE FORMULATION with BENZETHONIUM CHLORIDE ADMINISTERED by SUBCUTANEOUS INJECTION to RATS

CHARLES RIVER LABORATORIES PRECLINICAL SERVICES - OHIO
STUDY NUMBER: JIR00009

INTRODUCTION

The objective of this study was to compare the effects of 10% and 15% ketamine formulation with 0.002% benzalkonium chloride or 0.002% benzethonium chloride on neuronal degeneration in the retrosplenial cortex of the brain following a single subcutaneous injection. MK-801 was used as a positive control (for neuron degeneration within the retrosplenial cortex). Data from this study may also be used in the assessment of potential human risk and to select dose levels for a longer-term study. This report, prepared by Charles River Laboratories, Pathology Associates (PAI) – Maryland, for the testing facility, Charles River Laboratories Preclinical Services, Ohio, 640 N. Elizabeth Street, Spencerville, OH 45887, and the sponsor, Javelin Pharmaceuticals, Inc., 125 Cambridge Park Drive, Cambridge, MA 02140, presents the results of the evaluation of pathology endpoints. The portion of this study performed by PAI was conducted in the "spirit" of the most recent version of the FDA Good Laboratory Practice Regulations, 21 CFR Part 58.

EXPERIMENTAL DESIGN AND METHODS

According to the protocol, fifty (25 male and 25 female) Sprague Dawley rats were randomly divided into five groups as depicted in Text Table 1 – Study Design. Three groups were treated with Ketamine Hydrochloride, USP combined with one of two test article preservatives and sterile water for injection, USP as a vehicle. Rats in Group 5 (positive control) received MK-801 via subcutaneous injection once on Day 1.

Text Table 1. Study Design

Group Number	Number of Animals		Test Material	Dose Level (mg/kg)[b]	Perfusion Day
	Males	Females			
1	5	5	Saline	0	2
2	5	5	Ketamine w/ benzalkonium chloride (PMI-100)	60	2
3	5	5	Ketamine w/ benzethonium	60	2
4	5	5	Ketamine w/ benzalkonium chloride (PMI-150)	60	2
5	5	5	MK-801	0.5	2

On Day 2 all animals were anesthetized by an intraperitoneal injection of sodium pentobarbital and perfused with 10% neutral buffered formalin (NBF). The heads were then removed, placed in 10% NBF and sent to PAI's Frederick, MD facility where full-thickness coronal slices of approximately 2 millimeters thickness were prepared through three different levels of the retrosplenial cortex. These slices were embedded in paraffin, sectioned at 5 micrometers, and stained with Fluoro-Jade B. These sections were then examined with an epifluorescent microscope by the undersigned board-certified pathologist.

RESULTS

Early Deaths

There were no early deaths. All 50 animals survived until their scheduled sacrifice.

Gross Findings

Gross findings were not recorded during necropsy and therefore, are not discussed in this report.

Microscopic Pathology

Section II contains the data table generated from the microscopic evaluations. The microscopic findings were directly entered into a Microsoft® Office Excel (Version 2003 SP1) spreadsheet by the Study Pathologist. The following grading scheme was used: 1=minimal, 2=mild, 3=moderate and 4=marked. The quality of tissue fixation, processing, staining, and the accountability of tissues on slides were determined by the Study Pathologist to be fully acceptable for microscopic evaluation.

Although the microscopic evaluations were to be concentrated on the retrosplenial cortex, all portions of each section were examined and additional neuroanatomic regions added to the data table in order to show that rare individual degenerative neurons could be demonstrated (with the Fluoro-Jade stain) in regions other than the retrosplenial cortex. The other neuroanatomic regions present in the three sections were grouped into the following major categories: cerebral cortex, other; hippocampus; thalamus; hypothalamus; midbrain.

The only definitive treatment-related neuronal degeneration was present within the retrosplenial cortex of female rats treated with MK-801. All five of the female rats treated with MK-801 had minimal to mild multifocal neuron degeneration within the retrosplenial cortex. However, such degeneration was not present in the male rats treated with MK-801.

When examining Fluoro-Jade stained sections, rare degenerative neurons are occasionally encountered as background lesions. For example, one female rat in Group 1 (saline control) had one degenerating neuron in the temporal cortex. One male and one female rat in Group 3 (10% Ketamine with benzethonium chloride) had

single degenerative neurons within the dorsolateral portion of the retrosplenial cortical region immediately adjacent to the secondary visual cortex, but these rats had no evidence of degeneration within the medial region of the retrosplenial cortex (which is typically affected by MK-801). A similar finding was present for one male rat in Group 4 (15% Ketamine with benzalkonium chloride). The presence of single degenerative neurons in the same region of these three Ketamine-treated rats is of interest but of questionable biologic significance since only one degenerating neuron was present in each rat, and the more medial regions of the retrosplenial cortex (which are typically affected by MK-801) were not involved.

SUMMARY AND CONCLUSIONS

According to the protocol, fifty (25 male and 25 female) Sprague Dawley rats were randomly divided into five groups, three of which were treated with Ketamine Hydrochloride, USP combined with one of two test article preservatives and sterile water for injection, USP as a vehicle. The other two groups were a negative (saline-treated) group and a positive control group that received MK-801 *via* subcutaneous injection once on Day 1.

Definitive treatment-related lesions (neuronal degeneration within the retrosplenial cortex of the brain) were primarily limited to the female rats that had been treated with MK-801. These female rats had the expected pattern of neuronal degeneration within the medial aspect of the retrosplenial cortex.

Three rats treated with 60 mg/kg Ketamine Hydrochloride - two in Group 3 (with benzethonium chloride as the preservative) and one in Group 4 (with benzalkonium chloride as the preservative) - had single degenerative neurons within the dorsolateral portion of the retrosplenial cortex immediately adjacent to the secondary visual cortex. No rats in Group 2 (also treated with Ketamine having benzalkonium chloride as the preservative) had evidence of such neuronal degeneration. While the degenerative neurons within the retrosplenial cortices of the three affected Ketamine-treated rats were slightly more lateral than expected, the similar locations of the degenerative neurons in all three of these rats suggests that this neuronal degeneration is likely to represent a treatment effect. The higher frequency of neuron degeneration within the benzethonium chloride preservative group (*vs.* the two benzalkonium chloride preservative groups) suggests that benzalkonium chloride may be inherently less toxic than benzethonium chloride.

For example, Errando, *et al* have demonstrated that subarachnoid administration (to swine) of ketamine alone was not neurotoxic, whereas similar subarachnoid administration of ketamine together with benzethonium chloride or of benzethonium chloride alone produced evidence of neurotoxicity. The data from the present study supports the hypothesis that benzalkonium chloride may be less toxic than benzethonium chloride. However, the numbers of rats in this study and the numbers of degenerating neurons are too few to formulate a definitive conclusion.

STUDY PATHOLOGIST:

Robert H. Garman, DVM
Diplomate, ACVP,
Study Pathologist

25 May, 2006
Date

II. Microscopic Data Tables

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W
1	Dose	0 mg/kg Saline											60 mg/kg Ketamine w/benzalkonium chloride (PMI-100)										
2	Group	1											2										
3	Animal Number	6 6 2 4	6 6 2 5	6 6 2 6	6 6 2 7	6 6 2 8	6 6 4 9	6 6 5 0	6 6 5 1	6 6 5 2	6 6 5 3	INC	6 6 2 9	6 6 3 0	6 6 3 1	6 6 3 2	6 6 3 3	6 6 5 4	6 6 5 5	6 6 5 6	6 6 5 7	6 6 5 8	INC
4	Retrosplenial Cortex	N	N	N	N	N	N	N	N	N	N	10	N	N	N	N	N	N	N	N	N	N	10
5	NEURON DEGENERATION (FLUORO-JADE)	-	-	-	-	-	-	-	-	-	-	0	-	-	-	-	-	-	-	-	-	-	0
6	Cerebral Cortex, Other	N	N	N	N	N	N	N	-	N	N	9	N	N	N	N	N	N	N	N	N	N	10
7	NEURON DEGENERATION (FLUORO-JADE)	-	-	-	-	-	-	-	1)	-	-	1	-	-	-	-	-	-	-	-	-	-	0
8	Hippocampus	N	N	N	N	N	N	N	N	N	N	10	N	N	N	N	N	N	N	N	N	N	10
9	Thalamus	N	N	N	N	N	N	N	N	N	N	10	N	N	N	N	N	N	N	N	N	N	10
10	Hypothalamus	N	N	N	N	N	N	N	N	N	N	10	N	N	N	N	N	N	N	N	N	N	10
11	Midbrain	N	N	N	N	N	N	N	N	N	N	10	N	N	N	N	N	N	N	N	N	N	10

N=Normal; 1=Minimal; 2=Mild; 3=Moderate; 4=Marked; INC=Incidence;
< = multifocal; -=Not Applicable;)=focal

	A	X	Y	Z	AA	AB	AC	AD	AE	AF	AG	AH	AI	AJ	AK	AL	AM	AN	AO	AP	AQ	AR	AS	AT	AU	AV	AW	AX	AY	AZ
1	Dose	60 mg/kg Ketamine w/benzethonium chloride											60 mg/kg Ketamine w/benzalkonium chloride (PMI-150)											0.5 MK-801						
2	Group	3											4											5						
3	Animal Number	66334	66345	66356	66367	66383	66395	66406	66411	66426	66433	INC	66394	66404	66414	66424	66434	66445	66456	66466	66476	66486	INC	66447	66457	66467	66477	66487	66496	66507
4	Retrosplenial Cortex	N	N	N	N	-	N	N	-	N	N	8	N	-	N	N	N	N	N	N	N	N	9	N	N	N	N	N	-	-
5	NEURON DEGENERATION (FLUORO-JADE)	-	-	-	-	1)	-	-	1)	-	-	2	-	1)	-	-	-	-	-	-	-	-	1	-	-	-	-	-	1>	2>
6	Cerebral Cortex, Other	N	N	N	N	N	N	N	N	N	N	10	N	N	N	N	N	N	N	N	N	N	10	N	N	N	N	N	N	N
7	NEURON DEGENERATION (FLUORO-JADE)	-	-	-	-	-	-	-	-	-	-	0	-	-	-	-	-	-	-	-	-	-	0	-	-	-	-	-	-	-
8	Hippocampus	N	N	N	N	N	N	N	N	N	N	10	N	N	N	N	N	N	N	N	N	N	10	N	N	N	N	N	N	N
9	Thalamus	N	N	N	N	N	N	N	N	N	N	10	N	N	N	N	N	N	N	N	N	N	10	N	N	N	N	N	N	N
10	Hypothalamus	N	N	N	N	N	N	N	N	N	N	10	N	N	N	N	N	N	N	N	N	N	10	N	N	N	N	N	N	N
11	Midbrain	N	N	N	N	N	N	N	N	N	N	10	N	N	N	N	N	N	N	N	N	N	10	N	N	N	N	N	N	N

N=Normal; 1=Minimal; 2=Mild; 3=Moderate; 4=Marked; INC=Incidence;
< = multifocal; -=Not Applicable;)=focal

	A	BA	BB	BC	BD
1	Dose				
2	Group				
3	Animal Number	6667 1	6667 2	6667 3	INC
4	Retrosplenial Cortex	-	-	-	5
5	NEURON DEGENERATION (FLUORO-JADE)	1>	1>	2>	5
6	Cerebral Cortex, Other	N	N	N	10
7	NEURON DEGENERATION (FLUORO-JADE)	-	-	-	0
8	Hippocampus	N	N	N	10
9	Thalamus	N	N	N	10
10	Hypothalamus	N	N	N	10
11	Midbrain	N	N	N	10

N=Normal; 1=Minimal; 2=Mild; 3=Moderate; 4=Marked; INC=Incidence;
< = multifocal; -=Not Applicable;)=focal

Cell: AB5
Comment: 6638 Group 3 Male: A single degenerative neuron is present in the lateral portion of the retrosplenial cortex immediately adjacent to the seondary visual cortex.

Cell: AE5
Comment: 6661, Group 3 Female: Only one degenerative neuron is present, and this is relatively lateral, close to the secondary visual cortex.

Cell: AJ5
Comment: 6640 Group 4 Male: A single degenerative neuron is found in the most lateral portion of the retrosplenial cortex adjacent to the secondary visual cortex.

Cell: I7
Comment: 6651: One degenerating neuron is found in the temporal cortex.